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Synthesis and structure–activity relationships (SARs) of 1,5-diarylpyrazole cannabinoid type-1 (CB_1) receptor ligands for potential use in molecular imaging

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Abstract—Cannabinoid type-1 (CB_1) receptor ligands, derived from the 1,5-diarylpyrazole core template of rimonabant (Acomplia®), have been the focus of several studies aimed at examining structure–activity relationships (SARs). The purpose of this study was to design and synthesize a set of compounds based on the 1,5-diarylpyrazole template while focusing on the potential for discovery of CB_1 receptor radioligands that might be used as probes with in vivo molecular imaging. Each synthesized ligand was evaluated for potency as an antagonist at CB_1 and cannabinoid type-2 (CB_2) receptors in vitro using a GTPγ^{35}S-binding assay. clog *P* values were calculated with Pallas 3.0. The antagonist binding affinities (K_B) at CB_1 receptors ranged from 11 to >16,000 nM, CB_1 versus CB_2 selectivities from 0.6 to 773, and clog *P*s from 3.61 to 6.25. An interesting new ligand, namely *N*-(piperidin-1-yl)-1-(2-bromophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (**9j**), emerged from the synthesized set with appealing properties (K_B = 11 nM; CB_1 selectivity > 773; clog *P* = 5.85), for labeling with carbon-11 and development as a radioligand for imaging brain CB_1 receptors in vivo with positron emission tomography (PET).

1. Introduction

The medicinal and cognitive effects of Marijuana (*Cannabis sativa*) have been known for centuries. Despite its long history, only recently have studies provided convincing information on the biological mediation of its effects. Currently, in the endocannabinoid system, two sub-types of receptor, CB_1 and CB_2, are recognized as mediating the biological effects arising from exposure to receptor ligands, whether endogenous, plant-derived or synthetic receptor agonists, antagonists or inverse agonists.[1] Both CB_1 and CB_2 receptors belong to the G-protein-coupled superclass of receptors.[2] CB_1 receptors are located throughout the body including within the central nervous system (CNS)[3,4] at presynaptic nerve terminals and within the periphery at the intestine,[5] eye,[6] testis,[7] and bladder.[8] CB_2 receptors are mainly associated with cells of the immune system[9,10] (e.g., B-cells, natural killer cells, and monocytes). Brain CB_1 receptors represent an interesting target for the treatment of several psychiatric (e.g., anxiety,[11] addiction,[12] and depression[13]) and neurodegenerative disorders (e.g., Huntington's disease[14] and Tourette's syndrome[15]). The role of the CB_1 receptors in these disorders is not well understood. Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) coupled to an effective radioligand for CB_1 receptors might provide a further means for understanding the many such disorders linked to this receptor.

Molecular modification of the 1,5-diarylpyrazole core template of SR 141716A (*N*-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; rimonabant; Acomplia®; **1**, Table 1),[16] a potent and selective CB_1 receptor ligand, has been the focus of several studies aimed at uncovering the molecular requirements for CB_1 receptor antagonism or inverse agonism.[17–21] The pharmacophore derived from these studies has been previously reviewed.[20,22] This approach has led to the development of ligands with enhanced affinity and selectivity for the CB_1 receptor. The most notable of these ligands is AM 251 (*N*-(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-

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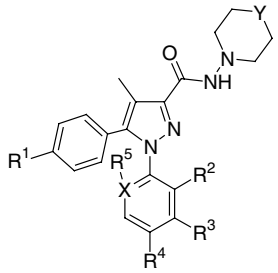
Table 1. Antagonist binding affinities, selectivities and calculated lipophilicities of 1,5-diarylpyrazole derivatives



Ligand	R^1	R^2	R^3	R^4	R^5	X	Y	CB_1 K_B[a] (nM)	CB_2 K_B[a] (nM)	CB_1 versus CB_2 selectivity	clog *P*	clog *D* at pH 7.4
1	Cl	Cl	H	Cl	H	C	CH_2	6.1	>6776	>1111	6.95	6.95
2	I	Cl	H	Cl	H	C	CH_2	3.8	904	238	7.36	7.36
3	I	Cl	H	H	H	C	O	8.9	1,069	120	5.66	5.66
4	MeO	Cl	H	Cl	H	C	CH_2	26	831	32	6.39	6.39
5	MeO	Cl	H	H	H	C	CH_2	25	2091	84	5.69	5.69
9a	MeS	Cl	H	H	H	C	CH_2	>3360	2091	<0.6	6.11	6.11
9b	$MeSO_2$	Cl	H	H	H	C	CH_2	302	>5770	>191	4.17	4.17
9c	MeO	H	H	Cl	H	C	CH_2	154	2868	19	5.69	5.69
9d	MeO	H	Cl	H	H	C	CH_2	>3884	>13,241		5.69	5.69
9e	MeO	H	H	H	H	C	CH_2	570	3471	6	5.05	5.05
9f	MeO	Cl	Cl	H	H	C	CH_2	140	510	3.6	6.24	6.24
9g	MeO	Cl	H	H	Cl	C	CH_2	270	1769	6.6	6.32	6.32
9h	MeO	Me	H	H	H	C	CH_2	55.9	4579	82	5.61	5.61
9i	MeO	Me	H	Me	H	H	CH_2	84.8	>16,908	>199	6.15	6.15
9j	MeO	Br	H	H	H	C	CH_2	11	>8500	>773	5.85	5.85
9k	MeO	CF_3	H	H	H	C	CH_2	51.6	2183	42	6.12	6.12
9l	MeO	H	H	H	—	N	CH_2	>4254	>16,908		4.39	4.39
9m	MeO	H	H	$MeSO_2$	H	C	CH_2	>3884	13,421	<3.5	3.61	3.61
9n	H	Cl	H	H	H	C	CH_2	532	2660	5	5.60	5.60
9o	OH	Br	H	H	H	C	CH_2	431	2744	6.4	5.34	5.02
9p	OH	Cl	H	H	H	C	CH_2	630	2261	3.6	5.18	4.85
9q	FCH_2O	Cl	H	H	H	C	CH_2	38	15,924	419	5.68	5.68

[a] These are single determinations run on plates with several control compounds. The inherent assay variability is about 3-fold.

1*H*-pyrazole-3-carboxamide; **2**, Table 1).[17,23] When compared to **1**, ligand **2** differs in the *para*-substituent on the C-5 aryl ring (I vs Cl, Table 1). An added benefit of **2** is its amenability for labeling with iodine-123, making it potentially useful for molecular imaging with SPECT.

Studies[23] with ^{123}I-labeled **2** have been disappointing because this radioligand does not enter the CNS sufficiently to be useful for SPECT imaging. The low brain entry of the radioligand has been ascribed[23,24] to the molecule's high lipophilicity (i.e., clog *P* = 7.36, Table 1). This conclusion prompted the development of AM 281 (*N*-(morpholin-4-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; **3**, Table 1),[24] an analog of AM 251 with lower lipophilicity (clog *P* = 5.66, Table 1). This ligand has also been labeled with iodine-123 and studied in Tourette's syndrome patients.[25] Other candidate radioligands that have been investigated are: [^{18}F]SR 144385,[26] [^{18}F]SR 147962,[26] [^{11}C]SR 149080,[27] [^{11}C]SR 149568,[27] and [^{11}C]NIDA 41087[21] [^{11}C]**5**, Table 1). However, none of these analogs has proven to be useful in molecular imaging.

The purpose of this study was to synthesize and characterize further ligands based on the 1,5-diarylpyrazole template with a view to discovering radioligands that might be used in the molecular imaging of brain CB_1 receptors with PET or SPECT. In addition to seeking desirable properties for molecular imaging in brain,[28] such as high affinity and high selectivity for CB_1 receptors plus an ability to enter brain, we also designed our target ligands to be amenable to labeling with a molecular imaging radionuclide, such as ^{11}C (β^+, $t_{1/2}$ = 20.4 min; ^{18}F (β^+, $t_{1/2}$ = 109.8 min), or ^{123}I (γ, $t_{1/2}$ = 13.2 h). Each target ligand was evaluated for binding affinity at both CB_1 and CB_2 receptors in vitro using GTPγ^{35}S-binding assays. For the purposes of clarification and comparison, a set of reference compounds (SR 141716A (**1**), AM 251 (**2**), AM 281 (**3**), NIDA 41020 (**4**), and NIDA 41087 (**5**), Table 1) were also evaluated in these assays. clog *P*, as an index of lipophilicity of each neutral microspecies, was calculated in order to provide an indication of each ligand's ability to cross the blood–brain barrier (BBB) without giving high non-specific binding. clog *D* values were also calculated at pH 7.4.

2. Results and discussion

2.1. Chemistry

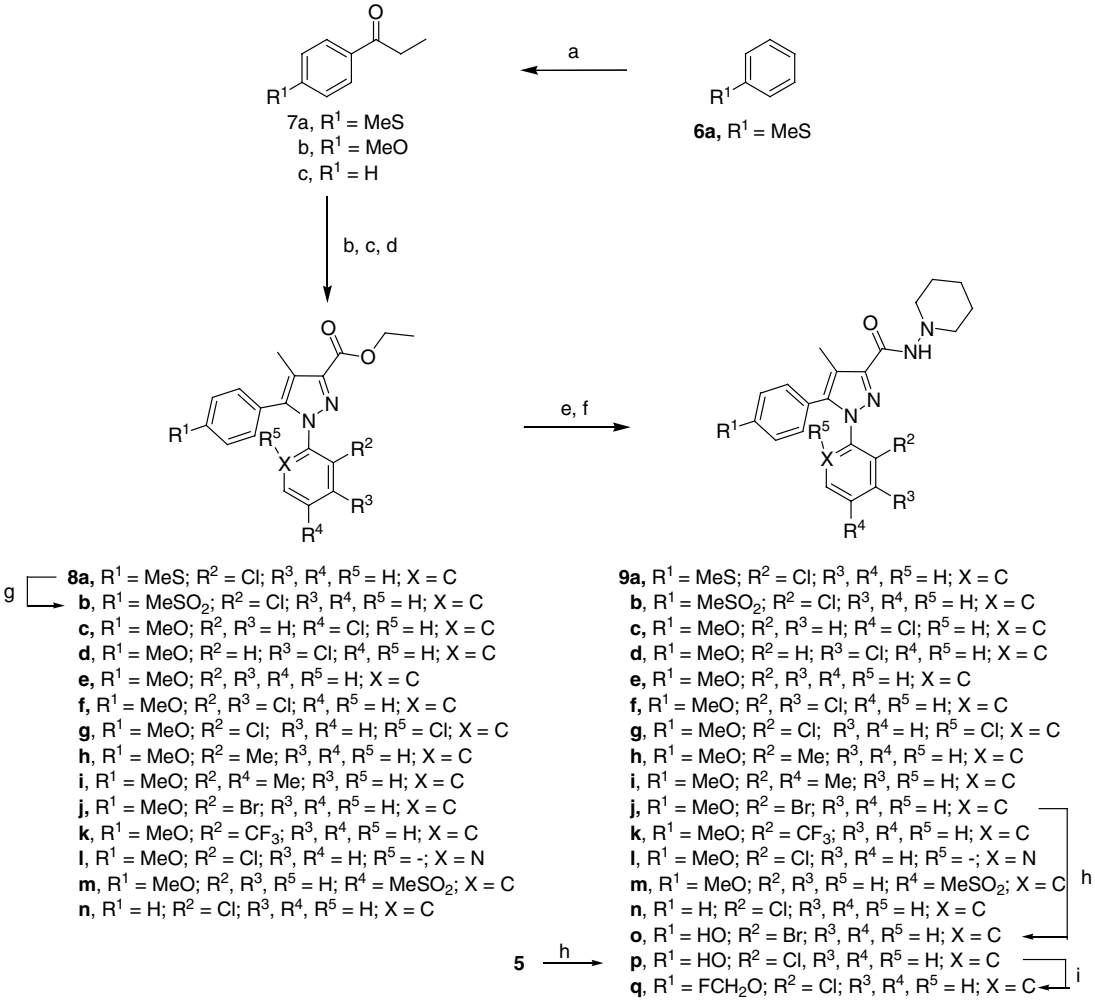
Compounds **9a**–**n** were synthesized according to a previously established procedure with some modifica-

tions.[17,21] The pathway for the synthesis of the 1,5-diarylpyrazole derivatives is outlined in Scheme 1. First, compound **7a** was prepared under Friedel–Crafts acylation conditions with aluminum chloride and propionyl chloride. Ketones **7a**–**c** were then condensed with diethyl oxalate in the presence of lithium diisopropylamide in ether at −78 °C. The resulting lithium salts were immediately reacted with various arylhydrazines in aqueous ethanol (70%) at room temperature (RT). Refluxing the resultant isolated hydrazones in acetic acid yielded the pyrazole carboxylic esters **8a**, **c**–**n**. Compound **8b** was prepared by oxidation of **8a** with *m*-chloroperoxybenzoic acid. Hydrolysis, conversion into the acyl chloride, and addition of the 1-aminopiperidine gave the desired carboxamides **9a**–**n**. Addition of boron tribromide to solutions of **9j** and **5** in dry dichloromethane adequately formed the phenols, **9o** and **9p**, respectively. Treating **9p** with fluoromethyl bromide in the presence of potassium carbonate in acetonitrile under microwave irradiation yielded the fluoromethoxy compound **9q**.

2.2. Structure–affinity relationships (SAR)

Research into the expansion of SAR information on compounds based on the 1,5-diarylpyrazole template began with modification of **4** and **5**. The reported[21] high-binding affinity and amenability to labeling of these compounds were initially intriguing. In order to gain further insights into the optimal substituents for the N-1 aryl ring, several compounds were prepared with variation of substituents in the R^2, R^3, R^4 and X positions. Table 1 shows the antagonist binding affinities (K_B) and selectivities for each of the synthesized candidate radioligands at CB_1 and CB_2 receptors. The reported K_B values for the CB_1 receptor ranged from 11 to >4224 nM and the selectivities ranged from <0.6 to >733. Most of the investigated compounds had little to no antagonist binding affinity for the CB_2 receptor. The K_B values for the CB_2 receptor ranged from 510 to >16,908 nM.

Switching the chlorine atoms from R^2 (**5**) to R^3 (**9d**) and R^4 (**9c**) reduced antagonist binding affinity (K_B = 25, >3884, and 154 nM, respectively) for the CB_1 receptor. This finding is consistent with results from other studies.[17] When all substituents were removed from the N-1 aryl ring (**9e**), there was a moderate loss of CB_1 receptor affinity (K_B = 570 nM). There was almost no CB_1 or CB_2 antagonist binding affinity when the X-position was replaced by a nitrogen (**9l**; K_B > 4254 nM).



Scheme 1. Reagents and conditions: (a) $AlCl_3$, DCE; (b) LDA, Et_2O, $(COEt)_2$; (c) R^2, R^3, R^4, R^5, X-ArN_2H_3·HCl, EtOH, rt; (d) AcOH, reflux; (e) Na_2O_2, MeOH; (f) $(COCl)_2$, DMF (cat), DCM, TEA, 1-aminopiperidine; (g) *m*-CPBA, DCM; (h) BBr_3, DCM; (i) FCH_2Br, K_2CO_3, microwave.

Dual chloro atoms in the R^2, R^3 and R^2, R^6 positions gave compounds **9f** and **9g** with moderate loss of CB_1 antagonist binding affinity (K_B = 140 and 270 nM, respectively). However, **9f** showed a higher antagonist binding affinity (K_B = 510 nM) for the CB_2 receptor. A total loss of CB_1 and CB_2 antagonist binding affinity (K_B > 3884 nM) was observed with a $MeSO_2$ group in the R^4-position (**9m**). These results suggested that the optimal position for improvement in CB_1 antagonist binding affinity is the R^2-position.

Varying the substituent in R^2-position with Me (**9h**) and CF_3 (**9k**) gave compounds with only a slight loss in CB_1 antagonist binding affinity (K_B = 55.9 and 51.6 nM, respectively) and almost no CB_2 receptor affinity. An additional Me group in the R^4-position (**9i**) lowered the CB_1 antagonist binding affinity relative to **9h** (K_B = 84.8 vs 55.9 nM). A 2-fold improvement in CB_1 antagonist binding affinity (K_B = 11 nM) was observed when a bromo group was incorporated into the R^2-position (**9j**), while CB_2 receptor antagonist binding affinity was virtually abolished (K_B > 16,908 nM).

Variations in the R^1-substituent of the 1,5-diarylpyrazole template were explored in order to determine the optimal SAR requirements in the R^1-position of the C-5 aryl ring. Surprisingly, when an MeS group (**9a**) replaced the MeO group (**5**) in the R^1-position, almost all of the CB_1 antagonist binding affinity (K_B > 3360 nM vs 25 nM) for the CB_1 receptor was lost. However, some CB_1 antagonist binding affinity (K_B = 302 nM) was regained when $MeSO_2$ (**9b**) replaced MeS (**9a**). There was reduced CB_1 antagonist binding affinity (K_B = 523 nM) with a hydrogen atom in the R^1-position (**9n**). There was also reduced antagonist binding affinity (K_B = 630 and 431 nM) with an OH-group in the R^1-position (**9o**, **p**, respectively). Placing a FCH_2O group (**9q**) in the R^1-position gave a compound with moderate antagonist binding affinity (K_B = 38 nM).

2.3. clog *P* and clog *D* determinations

Lipophilicity is an important but not always reliable parameter predicting a molecule's ability to pass the BBB and extent of non-specific binding in brain. Several studies aimed at relating molecular lipophilicity to BBB penetration have generated a parabolic curve in which the window for adequate brain entry lies between log *P* values of 1.5 and 3.5.[29] Molecules that lie outside this window are generally not considered to be useful for molecular imaging. However, the examined 1,5-diarylpyrazole radioligand, [^{123}I]AM 281, adequately enters the CNS with a clog *P* of 5.66 (Table 1) (measured log *P* = 4.3).[30] The clog *P* of the investigated ligands ranged from 3.61 to 7.36. With the exception of the phenols **9o** and **9p**, the prepared ligands **9a**–**q** have clog *D* (pH 7.4) values identical to their clog *P* values (Table 1). From the prepared set of ligands, the three compounds with attractive pharmacological properties, **5**, **9j**, and **9q**, have clog *P* values of 5.69, 5.89, and 5.68, respectively (Table 1), which are near or slightly higher than that of [^{123}I]AM 281. These compounds as radioligands may therefore be expected to enter the CNS to an extent similar to that of [^{123}I]AM281.

2.4. Prospective radioligands

Three ligands (**5**, **9j**, and **9q**) stand out as potential candidate PET radioligands for molecular imaging of brain CB_1 receptors. The preparation and in vitro autoradiography of [^{11}C]**5** have been reported previously.[31] However, the in vivo molecular imaging of this radioligand has not been reported. Ligand **9j** is similar to **5**, but has over a 2-fold greater antagonist binding affinity (K_B = 11 vs 25 nM). Ligand **9j** is also more selective than **5** (773- vs 84-fold) for CB_1 versus CB_2 receptors and is similarly amenable to labeling with carbon-11. The clog *P* values of **5** (clog *P* = 5.69) and **9j** (clog *P* = 5.89) are close to AM281 (clog *P* = 5.66), which represents a marker for acceptable CNS entry. Ligand **9q** benefits from the introduction of the fluoromethoxy group in the R^1-position, which provides an opportunity for labeling with fluorine-18. The antagonist binding affinity (K_B = 38 nM) of **9q** may however be too low to be useful for molecular imaging.

3. Conclusion

A set of new ligands was synthesized based on the 1,5-diarylpyrazole core template of SR 141716A (**1**). Pharmacological and physiochemical parameters (i.e., K_B values, selectivities, and lipophilicities) show **5**, **9j**, and **9q** to be interesting candidates for labeling with cyclotron-produced carbon-11 or fluorine-18. Further studies are proceeding to assess the suitability of these radioligands for molecular imaging in vivo.

4. Experimental

4.1. Materials

Ligands **1**, **4**, and **5** were synthesized according to previously established procedures.[17,21] **2** (AM251) and **3** (AM281) were obtained from Tocris (Ballwin, MO). Fluorobromomethane was purchased from ABCR GmbH & Co (Germany). All other reagents, including **7b** and **7c,** and solvents (ACS or HPLC grade) were purchased from commercial sources and used as supplied unless otherwise stated.

4.2. General methods

All reactions were carried out in an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. Melting points (uncorrected) were determined using a Melt-Temp apparatus (Dubuque; IA, USA). ^{1}H- (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker instrument (Billerica, MA, USA) for solution in $CDCl_3$ and DMSO-d_6 at 300 K, respectively, unless otherwise stated. ^{1}H NMR (300 MHz) spectra were recorded on a Varian Gemini (Palo Alto, CA, USA). Tetramethylsilane (TMS) was used as an internal standard in all cases and signals

are quoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentuplet) or m (multiplet). Chemical shift (δ) data for ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from the signal for TMS. The LC–MS analysis was performed on an LCQ Deca model LC–MS (Thermo Electron Corporation; San Jose, CA, USA). The chromatography was performed on a reverse-phase column (Luna C18; 150 (l) × 2 (id) mm; 5 μm; Phenomenex: Torrance, CA, USA). High-resolution mass spectra were determined using time-of-flight electrospray (University of Illinois at Urbana, Champain, IL, USA). Thin-layer chromatography (TLC) was carried out with silica gel 60 F254 plates (EM Science). Gradient flash chromatography was performed using a Horizon HPFC system (Biotage; Charlottesville, VA, USA). Elemental analyses were performed by (Quantitative Technologies Inc., Whitehouse, NJ). Compounds are indicated by their molecular formulae followed by the symbols for the elements measured (C, H, and N). Results are within 0.4% of their theoretical values.

4.3. clog *P* and clog *D* calculations

The clog *P* and clog *D* of ligands **1**–**5** and **9a**–**q** were determined from molecular structure using Pallas 3.0 software for Windows (CompuDrug International Inc.; South San Francisco, CA, USA).

4.4. Chemistry

4.4.1. 4′-(Methylthio)propiophenone (7a). Propionyl chloride (1.96 mL, 22.5 mmol) was added to a stirred solution of $AlCl_3$ (5.0 g, 37.5 mmol) in dichloromethane (50 mL) at 0 °C and stirring was continued for 10 min. Thioanisole (**6a**) (3.41 mL, 28.8 mmol) was then slowly added over 30 min. The mixture was allowed to warm to rt and stirred for 16 h. The mixture was then carefully poured onto crushed ice. The aqueous phase was extracted with dichloromethane (2× 50 mL). The organic phases were combined and washed with water (50 mL) and then aqueous $NaHCO_3$ (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified with silica gel chromatography (20% EtOAc–hexanes) to give **7a** (5.03 g; 70%); mp: 54–56 °C; ^{1}H NMR: 7.88 (d, J = 8 Hz, ArH), 7.26 (d, J = 8 Hz, ArH), 2.99 (q, J = 8 Hz, CH_2), 2.51 (s, SCH_3), 1.23 (t, J = 4 Hz, CH_3); ^{13}C NMR: 199.9, 145.5, 133.2, 128.4, 124.9, 31.6, 14.78, 8.33.

4.4.2. 1-(2-Chlorophenyl)-4-methyl-5-(4-methylthiophenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8a). A solution of **7a** (2.0 g, 11.1 mmol) in diethyl ether (10 mL) was added to a stirred solution of lithium diisopropylamide (7.4 mL; 1.8 M solution in THF) in diethyl ether (50 mL) at −78 °C. The reaction mixture was allowed to stir at −78 °C for a further 45 min. After the addition of diethyl oxalate (1.65 mL, 12.2 mmol), the reaction was stirred for 16 h while being allowed to warm to rt. The precipitate was filtered off, washed with diethyl ether (50 mL), and dried under vacuum. A portion of the lithium salt (1.0 g, 3.46 mmol) was suspended in ethanol (70%; 10 mL) and added to 2-chlorophenylhydrazine hydrochloride (616 mg, 3.46 mmol). The mixture was stirred at rt for 3 h. The precipitate was filtered off, washed with aqueous ethanol (70%; 5 mL), and dried under vacuum yielding a light yellow hydrazone. The hydrazone was dissolved in acetic acid (5 mL) and refluxed for 16 h. The reaction mixture was poured into ice-cold water (50 mL), neutralized with Na_2CO_3, and extracted with dichloromethane (3× 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. Purification with gradient flash chromatography (hexanes–ethyl acetate) gave the ester **8a** (856 mg; 64%); mp: 134–136 °C; ^{1}H NMR: 7.37 (d, J = 8 Hz, ArH), 7.33 (m, ArH), 7.15 (d, J = 8 Hz, ArH), 7.07 (d, J = 8 Hz, ArH), 4.48 (q, J = 8 Hz, CH_2), 2.45 (s, SCH_3), 2.37 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.3. 1-(2-Chlorophenyl)-4-methyl-5-(4-methanesulfonylphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8b). To a stirred solution of **8a** (300 mg, 777 μmol) in dichloromethane (20 mL) was added a solution of 77% 3-chloroperoxybenzoic acid (435 mg, 1.94 mmol) in dichloromethane (5 mL). The mixture was stirred for 18 h and then poured into aqueous $NaHCO_3$ (20 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2× 20 mL). The combined extracts were dried over $MgSO_4$, filtered and evaporated. Purification with gradient flash chromatography (hexanes–ethyl acetate) gave the ester **8b** (293 mg; 90%); mp: 168–170 °C; ^{1}H NMR: 7.89 (d, J = 8 Hz, ArH), 7.47 (d, J = 8 Hz, ArH), 7.38 (m, ArH), 4.49 (q, J = 8 Hz, CH_2), 3.07 (s, SO_2CH_3), 2.39 (s, CH_3), 1.4 (t, J = 4 Hz, CH_3).

4.4.4. 1-(3-Chlorophenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8c). The procedure described for the synthesis of **8a** was applied to **7c** and 3-chlorophenylhydrazine hydrochloride yielding **8c** (52%); mp: 112–114 °C; ^{1}H NMR: 7.45 (s, J = 8 Hz, ArH), 7.25 (d, J = 8 Hz, ArH), 7.18 (t, J = 8 Hz, ArH), 7.09 (d, J = 8 Hz, ArH), 7.06 (d, J = 8 Hz, ArH), 6.92 (d, J = 8 Hz, ArH) 4.49 (q, J = 8 Hz, CH_2), 3.83 (s, OCH_3), 2.29 (s, CH_3), 1.46 (t, J = 4 Hz, CH_3).

4.4.5. 1-Phenyl-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8d). The procedure described for the synthesis of **8a** was applied to **7c** and phenylhydrazine hydrochloride yielding **8d** (70%); mp: 164–166 °C; ^{1}H NMR: 7.30 (m, ArH), 7.09 (d, J = 8 Hz, ArH), 6.89 (d, J = 8 Hz, ArH), 4.48 (q, J = 8 Hz, CH_2), 3.80 (s, OCH_3), 2.31 (s, CH_3), 1.45 (t, J = 4 Hz, CH_3).

4.4.6. 1-(2,3-Dichlorophenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8e). The procedure described for the synthesis of **8a** was applied to **7c** and 2,3-dichlorophenylhydrazine hydrochloride yielding **8e** (67%); mp: 148–150 °C; ^{1}H NMR: 7.99 (d, J = 8 Hz, ArH), 7.52 (d, J = 8 Hz, ArH), 7.15 (t, J = 8 Hz, ArH), 7.04 (d, J = 8 Hz, ArH), 6.94 (d, J = 8 Hz, ArH), 4.23 (q, J = 8 Hz, CH_2), 3.77 (s, OCH_3), 1.57 (s, CH_3), 1.45 (t, J = 4 Hz, CH_3).

4.4.7. 1-(2,6-Dichlorophenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8f). The procedure for the synthesis of **8a** was applied to **7c** and 2,6-dichlorophenylhydrazine hydrochloride yielding **8f** (67%); mp: 108–110 °C; ^{1}H NMR: 7.33 (m, ArH), 7.18 (d, J = 8 Hz, ArH), 6.82 (d, J = 8 Hz, ArH), 4.48 (q, J = 8 Hz, CH_2), 3.77 (s, OCH_3), 2.33 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.8. 1-(2-Methylphenyl)-4-methyl-5-(4-methoxyphenyl)-1*H* -pyrazole-3-carboxylic acid, ethyl ester (8g). The procedure for the synthesis of **8a** was applied to **7c** and 2-methylphenylhydrazine hydrochloride yielding **8g** (52 %); mp: 149–150 °C; ^{1}H NMR: 7.24 (m, ArH), 7.04 (d, J = 8 Hz, ArH), 6.81 (d, J = 8 Hz, ArH), 4.47 (q, J = 8 Hz, CH_2), 3.76 (s, OCH_3), 2.36 (s, CH_3), 1.92 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.9. 1-(2,4-Dimethylphenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8h). The procedure for the synthesis of **8a** was applied to **7c** and 2,4-dimethylphenylhydrazine hydrochloride yielding **8h** (56%); mp: 88–90 °C; ^{1}H NMR: 7.12 (d, J = 8 Hz, ArH), 7.04 (d, J = 8 Hz, ArH), 6.97 (m, ArH), 6.82 (d, J = 8 Hz, ArH), 4.47 (q, J = 8 Hz, CH_2), 3.77 (s, OCH_3), 2.36 (s, CH_3), 2.29 (s, CH_3), 1.86 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.10. 1-(2-Trifluoromethylphenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8i). The procedure for the synthesis of **8a** was applied to **7c** and 2-(trifluoro)phenylhydrazine yielding **8i** (35%); mp: 134–136 °C; ^{1}H NMR: 7.71 (d, J = 8 Hz, ArH), 7.51 (m, ArH), 7.28 (d, J = 8 Hz, ArH), 7.06 (d, J = 8 Hz, ArH), 6.82 (d, J = 8 Hz, ArH), 4.47 (q, J = 8 Hz, CH_2), 3.76 (s, OCH_3), 2.33 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.11. 1-(2-Bromophenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8j). The procedure for the synthesis of **8a** was applied to **7c** and 2-bromophenylhydrazine hydrochloride yielding **8j** (49%); mp: 140–142 °C; ^{1}H NMR: 7.55 (d, J = 8 Hz, 1H), 7.39 (d, J = 7.39, 1H,), 7.34 (t, J = 8 Hz, 1H), 7.25 (t, J = 8 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 2H), 4.48 (q, J = 8 Hz, 2H), 3.77 (s, 3H), 2.35 (s, 3H), 1.44 (t, J = 8 Hz, 3H).

4.4.12. 1-(Pyridin-2-yl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8k). The procedure for the synthesis of **8a** was applied to **7c** and 2-pyridylphenylhydrazine yielding **8k** (26%); mp: 92–94 °C; ^{1}H NMR: 8.37 (d, J = 8 Hz, ArH), 7.73 (t, J = 8 Hz, ArH), 7.42 (d, J = 8 Hz, ArH), 7.28 (t, J = 8 Hz, ArH), 7.12 (d, J = 8 Hz, ArH), 6.90 (d, J = 8 Hz, ArH), 4.47 (q, J = 8 Hz, CH_2), 3.82 (s, OCH_3), 2.31 (s, CH_3), 1.44 (t, J = 4 Hz, CH_3).

4.4.13. 1-(4-Methanesulfonylphenyl)-4-methyl-5-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8l). The procedure for the synthesis of **8a** was applied to **7c** and 4-methansulfonylphenylhydrazine hydrochloride yielding **8l** (57%); mp: 136–138 °C; ^{1}H NMR: 7.87 (d, J = 8 Hz, ArH), 7.50 (d, J = 8 Hz, ArH), 7.10 (d, J = 8 Hz, ArH), 6.94 (d, J = 8 Hz, ArH), 4.49 (q, J = 8 Hz, CH_2), 3.86 (s, OCH_3), 3.09 (s, SO_2CH_3), 2.30 (s, CH_3), 1.46 (t, J = 4 Hz, CH_3).

4.4.14. 1-(2-Chlorophenyl)-4-methyl-5-phenyl-1*H*-pyrazole-3-carboxylic acid, ethyl ester (8m). The procedure for the synthesis of **8a** was applied to **7d** and 2-chlorophenylhydrazine hydrochloride yielding **8m** (56%); mp: 123–125 °C; ^{1}H NMR: 7.42 (d, J = 8 Hz, ArH), 7.39 (m, ArH), 7.17 (m, ArH), 6.80 (d, J = 8 Hz, ArH), 4.49 (q, J = 8 Hz, CH_2), 2.37 (s, CH_3), 1.45 (t, J = 4 Hz, CH_3).

4.4.15. *N*-(Piperidin-1-yl)-5-(4-methylthiophenyl)-1-(2-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9a). To a stirred solution of **8a** (400 mg; 1.04 mmol) in methanol (20 mL) was added Na_2O_2 (242 mg; 3.1 mmol). The mixture was stirred at rt for 3 h and then concentrated in vacuo. The residue was neutralized with HCl (10%), filtered, and dried under vacuum. A portion of the crude acid (200 mg, 558 μmol) was dissolved in dry dichloromethane (10 mL). To the stirred solution were added *N*,*N*-dimethylformamide (1 drop) and oxalyl chloride (73.1 μL, 838 μmol). After bubbling ceased, the reaction was concentrated in vacuo. A solution of 1-aminopiperidine (67 μL, 614 μmol) and triethylamine (118 μL, 838 μmol) in dichloromethane (10 mL) was slowly added to the acid chloride and stirred at rt for 2 h. Aqueous $NaHCO_3$ (50 mL) was added to the reaction flask and extracted with dichloromethane (3× 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated. Purification with gradient flash chromatography (hexanes–ethyl acetate) gave the carboxamide **9a** (83%) as a white solid; mp: 206–207 °C; ^{1}H NMR: 7.63 (d, J = 8.1 Hz, 2H, ArH), 7.56–7.50 (m, 2H, ArH), 7.42–7.40 (m, 2H, ArH), 7.33 (d, J = 8.1 Hz, 2H, ArH), 6.31 (br s, 1H, NH) 2.63 (t, J = 5.3 Hz, 4H, NCH_2), 2.54 (s, 3H, SCH_3), 2.43 (s, 3H, CH_3), 1.69 (p, J = 5.6 Hz, 4H, CH_2), 1.38–1.36 (m, 2H, CH_2); LC–MS, m/z $[M+H]^+$: 441.1; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{23}H_{26}N_4OClS$ = 441.1516. Found: 441.1525. Anal. ($C_{23}H_{25}N_4OClS$) C, H, N.

4.4.16. *N*-(Piperidin-1-yl)-5-(4-methanesulfonylphenyl)-1-(2-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9b). The procedure for the synthesis of **9a** was applied to **8b** yielding **9b** (84%) as a white solid; mp: 248–250; ^{1}H NMR: 7.06 (d, J = 8 Hz, 2H, ArH), 7.71 (br s, 1H, NH), 7.41–7.37 (m, 4H, ArH), 7.36 (d, J = 8 Hz, 2H, ArH), 3.08 (s, 3H, SO_2CH_3), 2.89 (t, J = 5.3 Hz, 4H, NCH_2), 2.45 (s, 3H, CH_3), 1.79 (p, J = 4 Hz, 4H, CH_2) 1.46–1.38 (m, 2H, CH_2); LC–MS, m/z $[M+H]^+$: 473.1; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{23}H_{26}N_4O_3ClS$ = 473.1414. Found: 473.1422. Anal. ($C_{23}H_{25}N_4O_3ClS$) C, H, N.

4.4.17. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9c). The procedure for the synthesis of **9a** was applied to**8c** yielding **9c** (79%) as a white solid; mp: 179–180 °C; ^{1}H NMR: 7.71 (br s, 1H, NH), 7.28 (d, 2H, J = 8 Hz, ArH), 7.18 (d, J = 8 Hz, 2H, ArH), 7.07 (d, J = 8 Hz, 2H, ArH), 6.9 (d, J = 8 Hz, 2H, ArH), 3.83 (s, 3H, OCH_3) 2.91

(t, $J = 5.3$ Hz, 4H, NCH_2), 2.33 (s, 3H, CH_3), 1.80 (p, $J = 5.6$ Hz, 4H, CH_2) 1.46–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 425.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{26}N_4O_2Cl$ 425.1744. Found: 425.1765. Anal. ($C_{23}H_{25}N_4O_2Cl$) C, H, N.

4.4.18. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(3-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9d). The procedure for the synthesis of **9a** was applied to **8d** yielding **9d** (87%) as a white solid; mp: 61–62 °C; ^{1}H NMR: 7.73 (br s, 1H, NH), 7.41 (t, $J = 4$ Hz, 1H, ArH), 7.36 (m, 3H, ArH), 7.08 (d, $J = 8$ Hz, 2H, ArH), 6.92 (d, $J = 8$ Hz, 2H, ArH), 3.86 (s, 3H, OCH_3) 2.89 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.33 (s, 3H, CH_3), 1.77 (p, $J = 6$ Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 425.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{26}N_4O_2Cl$ 425.1744. Found: 425.1748. Anal. ($C_{23}H_{25}N_4O_2Cl{\cdot}0.5H_2O$) C, H, N.

4.4.19. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(phenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9e). The procedure for the synthesis of **9a** was applied to **8e** yielding **9e** (79%) as a white solid; mp: 164–165; ^{1}H NMR: 7.63 (br s, 1H, NH), 7.31–7.20 (m, 6H, ArH), 7.08 (d, $J = 8$ Hz, 2H, ArH), 6.89 (d, $J = 8$ Hz, 2H, ArH), 3.81 (s, 3H, OCH_3) 2.86 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.34 (s, 3H, CH_3), 1.79 (p, $J = 6$ Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 391.2; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{27}N_4O_2$ 391.2134. Found: 391.2143. Anal. ($C_{23}H_{26}N_4O_2$) C, H, N.

4.4.20. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(2,3-dichlorophenyl)-4-methyl- 1*H*-pyrazole-3-carboxamide (9f). The procedure for the synthesis of **9a** was applied to **8f** yielding **9f** (91%) as a white solid: mp: 194–195 °C; ^{1}H NMR: 7.64 (br s, 1H, NH), 7.51–7.27 (t, $J = 7.51$, 1H, ArH), 7.3–7.23 (m, 4H, ArH) 7.06 (d, $J = 8$ Hz, 2H, ArH), 6.83 (d, $J = 8$ Hz, 2 H, ArH), 3.78 (s, 3H, OCH_3) 2.86 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.36 (s, 3H, CH_3), 1.76 (p, $J = 5.6$ Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 459.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{25}N_4O_2Cl_2$ 459.1355, Found: 459.1363. Anal. ($C_{23}H_{24}N_4O_2Cl_2{\cdot}0.4H_2O$) C, H, N.

4.4.21. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(2,6-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9g). The procedure for the synthesis of **9a** was applied to **8g** yielding **9g** (75%) as a white solid: mp: 214–216 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.63 (br s, 1H, NH), 7.34–7.24 (m, 3H, ArH), 7.16 (d, $J = 8$ Hz, 2H, ArH), 6.84 (d, $J = 8$ Hz, 2H, ArH), 3.77 (s, 3H, OCH_3), 2.89 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.36 (s, 3H, CH_3), 1.77 (p, $J = 6$ Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 459.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{25}N_4O_2Cl_2$ 459.1355, Found: 459.1369. Anal. ($C_{23}H_{24}N_4O_2Cl_2{\cdot}0.4H_2O$) C, H, N.

4.4.22. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(2-methylphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9h). The procedure for the synthesis of **9a** was applied to **8h** yielding **9h** (89%) as a white solid: mp: 204–205 °C; ^{1}H NMR: 7.80 (br s, 1H, NH), 7.8–7.27 (m, 4H, ArH), 7.13 (d, $J = 8$ Hz, 2H, ArH), 6.90 (d, $J = 8$ Hz, 2H, ArH), 3.87 (s, 3H, OCH_3) 2.97 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.50 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.89 (p, $J = 5.6$ Hz, 4H, CH_2) 1.55–1.48 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 405.2; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{24}H_{29}N_4O_2$ 405.2291. Found: 405.2304. Anal. ($C_{24}H_{29}N_4O_2$) C, H, N.

4.4.23. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(2-trifluoromethylphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9i). The procedure for the synthesis of **9a** was applied to **8i** yielding **9i** (84%) as a white solid: mp: 196 °C; ^{1}H NMR: 7.78 (d, $J = 8$ Hz, 1H, ArH), 7.50 (m, 2H, ArH), 7.14 (d, $J = 8$ Hz, 1H, ArH), 7.04 (d, $J = 8$ Hz, 2H, ArH), 6.81 (d, $J = 8$ Hz, 2H, ArH), 3.76 (s, 3H, OCH_3) 2.86 (t, $J = 5.1$ Hz, 4H, NCH_2), 2.37 (s, 3H, CH_3), 1.77 (p, $J = 5.4$ Hz, 4H, CH_2) 1.44–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 459.2. Anal. ($C_{23}H_{25}F_3N_4O_2$) C, H, N.

4.4.24. *N*-(Piperidin-1-yl)-1-(2-bromophenyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9j). The procedure for the synthesis of **9a** was applied to **8j** yielding **9j** (87%) as a white solid: mp: 204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.7 (br s, 1H, NH), 7.60 (d, $J = 9$ Hz, 1H, ArH), 7.33–7.21 (m, 3H, ArH), 7.06 (d, $J = 5.1$ Hz, 2H, ArH), 6.81 (d, $J = 5.1$ Hz, 2H, ArH), 3.76 (s, 3H, OCH_3) 2.86 (t, $J = 5.1$ Hz, 4H, NCH_2), 2.37 (s, 3H, CH_3), 1.77 (p, $J = 5.4$ Hz, 4H, CH_2) 1.44–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 469.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{23}H_{25}BrN_4O_2$ 469.1239, Found: 469.1232. Anal. ($C_{23}H_{25}BrN_4O_2$) C, H, N.

4.4.25. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(2,4-dimethylphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9k). The procedure for the synthesis of **9a** was applied to **8k** yielding **9k** (89%) as a white solid: mp: 132–133 °C; ^{1}H NMR: 7.71 (br s, 1H, NH), 7.10 (d, $J = 8$ Hz, 1H, ArH) 7.03–6.99 (m, 4H, ArH), 6.81 (d, $J = 8$ Hz, 2H, ArH), 3.77 (s, 3H, OCH_3) 2.84 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.37 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 1.77 (p, $J = 5.6$ Hz, 4H, CH_2) 1.45–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 419.2; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{25}H_{31}N_4O_2$ 419.2447. Found: 419.2462; Anal. ($C_{25}H_{31}N_4O_2{\cdot}0.5H_2O$) C, H, N.

4.4.26. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-pyridin-2-yl-4-methyl-1*H*-pyrazole-3-carboxamide (9l). The procedure for the synthesis of **9a** was applied to **8l** yielding **9l** (86%) as a white solid: mp: 170–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.46 (d, $J = 8$ Hz, 1H, NH), 7.8 (br s, 1H, NH), 6.7 (t, $J = 9.6$ Hz, 1H, ArH) 7.25–7.16 (m, 4H, ArH), 7.11 (d, $J = 8$ Hz, 2H, ArH), 6.89 (d, $J = 8$ Hz, 2H, ArH), 3.82 (s, 3H, OCH_3) 2.90 (t, $J = 5.3$ Hz, 4H, NCH_2), 2.35 (s, 3H, CH_3), 1.79 (p, $J = 5.6$ Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS, *m/z* $[M+H]^+$: 392.1; HRMS Calcd *m/z* (TOF) $[M+H]^+$: $C_{22}H_{25}N_5O_2$ 392.2087. Found: 392.2093; Anal. ($C_{22}H_{24}N_5O_2$) C, H, N.

4.4.27. *N*-(Piperidin-1-yl)-5-(4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9m). The procedure for the synthesis of **9a** was applied

to **8m** yielding **9m** (85%) as a white solid: mp: 218–220 °C; ^{1}H NMR: 7.88 (d, J = 12 Hz, 2H, ArH), 7.73 (br s, 1H, NH), 7.46 (d, J = 12 Hz, 2H, ArH), 7.10 (d, J = 8 Hz, 2H, ArH), 6.94 (d, J = 8 Hz, 2H, ArH), 3.85 (s, 3H, OCH_3), 3.05 (s, 3H, SO_2CH_3), 2.9 (t, J = 5.3 Hz, 4H, NCH_2), 2.33 (s, 3H, CH_3), 1.77 (p, J = 6 Hz, 4H, CH_2) 1.47–1.38 (m, 2H, CH_2); LC–MS, m/z $[M+H]^+$: 469.2; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{24}H_{29}N_4O_4S$ 469.1910. Found: 469.1915; Anal. ($C_{24}H_{28}N_4O_4S$) C, H, N.

4.4.28. *N*-(Piperidin-1-yl)-5-phenyl-1-(2-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9n). The procedure for the synthesis of **9a** was applied to **8n** yielding **9n** (89%) as a white solid: mp: 224–225 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (br s, 1H, NH), 7.31 (m, 5H, ArH), 7.07 (d, J = 5.1 Hz, 2H, ArH), 6.80 (d, J = 5.1 Hz, 2H, ArH), 3.80 (s, 3H, OCH_3) 2.89 (t, J = 5.1 Hz, 4H, NCH_2), 2.35 (s, 3H, CH_3), 1.79 (p, J = 5.4 Hz, 4H, CH_2) 1.45 (m, 2H, CH_2); LC–MS m/z $[M+H]^+$: 395.1; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{22}H_{24}N_4O_2Cl$ 395.1639. Found: 365.1649. Anal. ($C_{22}H_{23}N_4O_2Cl$) C, H, N.

4.4.29. *N*-(Piperidin-1-yl)-1-(2-bromophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9o). To a stirred solution of **9j** (500 mg; 1.07 mmol) in dry dichloromethane (20 mL) was added BBr_3 (5.89 mL; 1 M solution in dichloromethane). The reaction was stirred at rt for 3 h. The reaction was quenched with careful addition of methanol. The combined extracts were dried over $MgSO_4$, filtered and evaporated. The product was purified with flash chromatography (chloroform–methanol 10%) yielding **9o** (407 mg, 84%) as a white solid: mp: 260–262 °C; ^{1}H NMR (DMSO-d_6): 11.7 (br s, 1H, NH), 7.71 (m, 4H, ArH), 7.04 (d, J = 8 Hz, 2H, ArH), 6.73 (d, J = 8 Hz, 2H, ArH), 2.49 (t, J = 5.1 Hz, 4H, NCH_2), 2.26 (s, 3H, CH_3), 1.85 (p, J = 5.4 Hz, 4H, CH_2) 1.49 (m, 2H, CH_2); LC–MS m/z $[M+H]^+$: 455.0; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{22}H_{24}N_4O_2Br$ 455.1083. Found: 455.1104. Anal. ($C_{22}H_{23}N_4O_2Br$) C, H, N.

4.4.30. *N*-(Piperidin-1-yl)-1-(2-chlorophenyl)-5-(4-hydroxyphenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9p). The demethylation procedure applied in the synthesis of **9o** was applied to carboxamide **5** (500 mg; 1.18 mmol) yielding **9p** (92%) as a white solid: mp: 256–257 °C; ^{1}H NMR (DMSO-d_6): 11.7 (br s, 1H, NH), 7.71 (m, 4H, ArH), 7.05 (d, J = 8 Hz, 2H, ArH), 6.76 (d, J = 8 Hz, 2H, ArH), 2.56 (t, J = 5.1 Hz, 4H, NCH_2), 2.30 (s, 3H, CH_3), 1.91 (p, J = 5.4 Hz, 4H, CH_2) 1.45 (m, 2H, CH_2); LC–MS, m/z $[M+H]^+$: 411.1; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{22}H_{24}N_4O_2Cl$ 411.1588. Found: 411.1596; Anal. ($C_{22}H_{23}N_4O_2Cl$) C, H.

4.4.31. *N*-(Piperidin-1-yl)-5-(4-fluoromethoxyphenyl)-1-(2-chlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (9q). To a stirred solution of carboxamide **9p** (200 mg, 488 μmol) and K_2CO_3 (134 mg, 975 μmol) in acetonitrile (2 mL) cooled to 0 °C in a sealed microwave vial was added fluoromethyl bromide (251 mg, 2.24 mmol). The reaction was irradiated in a single mode microwave cavity for 20 min at 150 °C using 100 W. The reaction solution was poured in the water (20 mL) and extracted with dichloromethane (2× 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification with gradient flash chromatography (hexanes–ethyl acetate) gave **9q** as a white solid (34 mg, 16%); mp: 201–203 °C; ^{1}H NMR: 7.69 (br s, 1H, NH), 7.48–7.35 (m, 4H, ArH), 7.11 (d, J = 8 Hz, 2H, ArH), 6.81 (d, J = 8 Hz, 2H, ArH), 5.75 (d, J = 52, 2H, OCH_2F) 2.86 (t, J = 5.3 Hz, 4H, NCH_2), 2.37 (s, 3H, CH_3), 1.77 (p, J = 6 Hz, 4H, CH_2) 1.48–1.38 (m, 2H, CH_2); LC–MS m/z $[M+H]^+$: 443.1; HRMS Calcd m/z (TOF) $[M+H]^+$: $C_{23}H_{25}N_4O_2FCl$ 443.1650. Found: 443.1660; Anal. ($C_{23}H_{24}N_4O_2FCl$) C, H, N.

4.5. CB_1 and CB_2 GTPγ ^{35}S-binding assays

GTPγ^{35}S binding was measured in a 96-well format, using a modified antibody capture technique previously described.[32] Test compounds were diluted in GTP-binding assay buffer (20 mM Hepes, 100 mM NaCl, and 5 mM $MgCl_2$, pH 7.4) containing bovine serum albumin (0.5%). Sf9 cell membranes, expressing human CB_1 or CB_2 receptors, and Gai3b1g2 (Perkin Elmer, Boston, MA, USA) in GTP-binding assay buffer and the test compound were incubated for 15 min at rt. This was followed by the addition of GTPγ^{35}S (500 pM; NEN, Boston, MA) and a 35 min incubation. The labeled membranes were then solubilized with 0.27% Nonidet P40 detergent (Roche, Indianapolis, IN) and incubated for 30 min. Rabbit anti-Gai3 antibody was then added at a final dilution of 1:300 and the mixture was incubated for another 30 min. Anti-rabbit antibody-coated scintillation proximity assay beads (Amersham Life Sciences, Arlington Heights, IL) were added and the plates were incubated at RT for an hour. The plates were then centrifuged at 180g for 10 min using a Beckman GS-6R centrifuge and counted for 1 min per well using a Wallac 1450 MicroBeta TriLux scintillation counter (Perkin Elmer Life Sciences, Wallac Inc., Gaithersburg, MD). Agonist EC_{50} values and antagonist IC_{50} values were calculated with Activity Base software using a four-parameter fit and K_B values (binding constants) calculated as follows: $K_B = IC_{50}/[1 + [\text{Agonist}]/EC_{50}]$.

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